REMARKS

Claim 1 has been amended by limiting the source of testis to one obtained from an adult avian aged up to 70 weeks. Support for this amendment can be found throughout the specification, in particular page 5, lines 17-21 of the specification. Thus, no new matter is added into claim 1. Applicants further note the addition of new claim 20, which specifies that the avian testis from which testicular cells are isolated according to the invention are from an avian aged 2-70 weeks; new claim 21, which specifies that the avian of claim 20 is aged up to 20 weeks; new claim 22, which specifies that the avian of claim 21 is aged 2-10 weeks; claims 23 and 24, which specify that the avian of claims 20 and 22 is a chicken; and claim 25, which specifies that the avian is not in an embryonic stage. No new matter has been added.

The preceding amendments and the following remarks are believed to be fully responsive to the outstanding Office Action and are believed to place the application in condition for allowance.

The Examiner is respectfully requested to reconsider and withdraw the rejections in view of the amendments and remarks as set forth hereinbelow.

I. Rejection under 35 U.S.C. § 102

With regard to the rejection under 35 U.S.C. § 102, the Examiner has alleged that the instant inventions of claims 1, 2, 4-10, 12, 13, and 14 are anticipated by the reference of Baguisi et al. (U.S. Patent Publication No. 2002/0162134). This rejection is respectfully traversed.

The Examiner states in the rejection reason that the claims do not require the testis to be of any particular stage of development. Therefore, in order to overcome the rejection, the testis

of the present claim 1 has been limited to the avian testis that is prepared from adult avian aged up to 70 weeks. By this amendment, it is clearly specified that the avian spermatogonial stem cells in the present claim 1 are prepared from the avian testis of adult avian aged up to 70 weeks.

Consequently, Applicants respectfully requests that this rejection be withdrawn.

II. Rejection under 35 U.S.C. § 103

The Examiner rejected claims 1, 3, 11, and 15 as being unpatentable over Baguisi et al. in view of Shinohara et al. (U.S. Patent Publication No. 2006/0265774). This rejection is respectfully traversed.

Applicants repeatedly emphasizes that the reference of Baguisi et al. discloses the method of preparing primordial gonad cells (PGCs) from the gonad originated from chicken embryo not from the testes of adult.

The Examiner asserted that the reference of Baguisi et al. teaches the method of isolating sperm stem cells from testes based on the description of "the invention features an isolated avian gonadal cell, e.g., an ovarian or a testes cell, containing a heterologous nucleic acid" in Abstract and paragraph of [0004], and claim 5. However, please note that there is no substantial description as to specific procedures to actually isolate or prepare sperm stem cells from the testes of adult chicken in the Baguisi reference. In other words, although the reference of Baguisi et al. just merely mentions the testis cells as an example of an isolated avian gonadal cell, there is no substantial description as to isolate sperm stem cells from the testis originated from adult male chicken. The entire context of Baguisi makes it clear that embryonic cells alone, and not adult cells, are contemplated for use in the method of Baguisi.

In response to our arguments that no description of actually obtaining spermatogonial cells from testes can be found in the Baguisi et al. reference, the Examiner indicated that paragraphs [0049]-[0050] describe the preparation procedure of sperm stem cells from testes. However, please note that it is evident that the germ cells in the isolation procedures in paragraphs [0049]-[0050] are originated from chicken embryonic gonad not from adult male chicken testis in view of that the contents of paragraphs [0049]-[0050] is a continuation of the preceding paragraphs [0046]-[0048], in which gonads are isolated from chick embryo between days 4-8. In addition, it is noteworthy that it is described in paragraph [0050] indicated by the Examiner that "the isolated gonads were grouped by sex" and in preceding paragraph [0047] that "the gonads were recovered by removing the mesonephros region from the abdominal cavity of the embryos and dissecting out the gonads from the mesonephros using fine tip forceps under low power magnification. At 7-7.5 days of incubation, developmental differences between the differentiating female and male gonads can be identified allowing for sex selection." The above descriptions explicitly reveal that isolated gonads in paragraph [0050] are originated from the chicken embryos not from adult male testes because if the gonads are prepared from the adult testes, the grouping step of the isolated gonads according to their sex are not required.

Accordingly, it is evident that the reference of Baguisi et al. does not teach the isolation spermatogonial stem cells (SSCs) from the testes of adult avian aged up to 70 weeks, rather it does teach the isolation of primordial germ cells (PGCs) from chicken embryo.

Meanwhile, it is evidently clear that the reference of Shinohara et al. does not disclose the limitation of the presently amended claim 1, that is the step (a) referring the preparation of an *avian* testis from an adult avian aged up to 70 weeks.

The reference of Shinohara et al. discloses the method of isolating mammalian spermatogonial stem cells (SSCs) from mammalian testes, especially from mouse testes.

As evidently explained in the above, the teaching of Baguisi et al. is the method of isolating and culturing primordial gonad cells (PGCs) from chick embryo not from adult chick testes, and the teaching of Shinohara et al. is the method of isolating and culturing mammalian (especially, mouse) spermatogonial stem cells (SSCs) from mammalian (especially, mouse) testes.

The patentability of the presently amended claim 1 should be determined based on whether the combination of the teachings of the references of Baguisi et al. and Shinohara et al. make it obvious or not to arrive at the invention of the present claim 1. Specifically, the point of the determining the obviousness of the present claim 1 is whether the teaching of the method of isolating and culturing of mammalian SSCs can be properly combined with the teaching of the method of isolating and culturing embryonic chicken PGCs in order to reach the invention of present claim 1 referring the method of isolating and culturing avian SSCs from the testes of adult avian.

The Examiner asserts that it would have been *prima facie* obvious for a person of ordinary skill in the art to combine the teachings of Baguisi et al. and Shinohara et al. to isolate sperm stem cells from an avian testis with reasonable expectation of success at the time of the instant invention as both describe methods for the preparation and culture of sperm stem cells.

However, according to MPEP 2143.01, the mere fact that references can be combined or modified does not render the resultant combination obvious unless the results would have been predictable to one of ordinary skill in the art. The results of the present invention would not have

been predictable, based on the cited references.

In this regard, please note that in paragraph [0003] of page 1 of the reference of Baguisi et al. it is described that "some researchers have reported the production of cloned animals by nuclear transfer in mammals, e.g., sheep (Wilmut et al. 1997, Nature 385:810-813), cows (Cibelli et al. 1998, Science 280: 1256-1258), mice (Wakayama et al., 1998 Nature 394: 369-394) and goats (Baguisi et al. 1999, Nature Biotechnology 17: 456-461) using somatic cells as donor karyoplast. However, these techniques are still in their early developmental stage and may be difficult to adapt to the uniquely different reproductive systems of birds." This passage clearly supports the unpredictability of the present invention.

According to the above-indicated description, Baguisi et al. explicitly reveals that the techniques developed in the mammalian systems such as in sheep, cows, mice, and goats are remarkably difficult to apply to the bird system because the reproductive systems of mammals and birds are distinctly different. Although the technique that is mentioned in the Baguisi et al. reference paragraph [0003] is nuclear transfer by using somatic cells, it is well known in the art that the method of isolating and culturing sperm stem cells developed in the mammalian system is difficult to adapt to the avian system since the morphology, structure, and location of testes of avian is greatly different from those of mammalian, especially mouse.

Accordingly, the reference of Baguisi et al. does not explicitly or implicitly suggest any desirability or advantage of combining the teaching of Shinohara et al. (SSCs isolation and culture in mammalian system) to arrive at the invention of present claim 1, and certainly does not make the result of the invention of the present claims predictable. On the contrary, Baguisi et al. teaches away from the combination of the teachings in the reference of Baguisi et al. with

Shinohara et al. in view of the above description in the last sentence of paragraph [0003] of Baguisi et al.

In addition to the descriptions of Baguisi et al., in paragraphs [0006] of the reference of Shinohara et al. it is described that "However, in any animal other than mice (for example, domestic animals such as swine and bovines and primates), no ES cells capable of producing germ cells have been collected to date, nor is there any report of knockout achieved by this technique." Further, in paragraphs [0007] of the reference of Shinohara et al. it is described that "For animals other than mice, however, the success rate (of gene injection) is very low (for example, around 1% for swine and 1% or less for bovines) and the method is very expensive and unrealistic."

Further, in paragraph [0010] below of the reference of Shinohara et al. describing the conventional techniques of isolating and culturing spermatogonial stem cells, there is no description as to any other animal stem cell than mouse or rat spermatogonial stem cells.

Paragraph [0010] of the reference of Shinohara et al

> [Specifically, with the method described in "Nagano M, Avarbock M R, Leonida E B, Brinster C J, Brinster R L, Culture of **mouse** spermatogonial stem cells, Tissue Cell, 1998, Vol. 30, pp. 389-397", spermatogonial stem cells reportedly survived in vitro for 3 months or more, but no evidence for stem cell proliferation is given. Additionally, the methods of cultivation described in Japanese Patent Kohyo Publication No. 2001-517927, "Feng L-X, Chen Y, Dettin L, Reijo Pera R A, Herr J C, Goldberg E, Dym M, Generation and in vitro differentiation of a spermatogonial cell line, Science, 2002, Vol. 297, pp. 392-395", "van Pelt A M M, Roepers-Gajadien H L, Gademan I S, Creemers L B, de Rooij D G, van Dissel-Emiliani F M F, Establishment of cell lines with **rat** spermatogonial stem cell characteristics, Endocrinology, 2002, Vol. 143, pp. 1845-1850" and the like are problematic in that extraneous genes cannot be stably introduced to spermatogonial stem cells, and are also problematic in that no offspring derived from the spermatogonial stem cells cannot be obtained. Although spermatogonial stem cells can survive when cultured in vitro using one of the above-described methods of cultivation, the number of cells decreases to about 20% of the original number in 1 week under the present situation, and it is impossible to grow the cells. Hence, the

conventional techniques are subject to limitation in manipulating spermatogonial stem cells to apply for biotechnology and the like. Additionally, no cases of actual spermatogenesis using spermatogonial stem cells cultured in vitro persistently for a long time have been reported to date.]

The above-indicated descriptions of Shinohara et al. explicitly confirm the well known fact in the art that the feasibility of the techniques used in the field of stem cells is strongly dependent upon what animal system is utilized and the success rate of stem cell culture in other animal systems than a well established mouse system is significantly low.

Applicants thus submit that the reference of Shinohara et al., when considered with Baguisi, does not make the present invention predictable. They also do not sufficiently suggest the desirability, advantage, or motivation to adapt their method of isolating and culturing SSCs obtained from mouse testes to avian system.

M.P.E.P. 2143.02 (I) states "the prior art can be modified or combined to reject claims as prima facie obvious as long as there is a reasonable expectation of success."

From the descriptions of Shinohara et al. at paragraph [0006] and [0007], there is no description as to reasonable expectation of success of application of the technique of isolation and culture of SSCs in mouse system to avian system.

In view of the above sufficient explanation provided by Applicants, no reason, suggestion, or motivation can be found in the prior art to combine the teachings of the references of Baguisi et al. and Shinohara et al. to arrive at the presently claimed invention. Accordingly, denying the unobviousness of the present claims over Baguisi et al. and Shinohara et al. must be a result of the improper hindsight reconstruction of the presently claimed invention.

To further support the non-obviousness of the present invention, Applicants submit the

accompanying Declaration of Jae Yong Han, an inventor named on the application. In the Declaration, inventor Han explains that the development of methods for the long-term culture of SSCs from the avian testes satisfies a long but unresolved need, and thus provides evidence supporting secondary indicia of non-obviousness of the present invention. Inventor Han explains the importance of the development of avian SSC culture methods, benefits of SSCs over PGCs, and reasons why methods for isolating and culturing SSCs from mice would not be predictive of success in isolating and culturing avian SSCs.

In summary, the references of Baguisi et al. and Shinohara et al. do not explicitly or implicitly suggest any desirability or advantage of combining the teachings of the references to arrive at the invention of the present claims with reasonable expectation of success. On the contrary, the reference of Baguisi et al. teaches away from the combination of the teachings in the reference of Baguisi et al. with Shinohara et al. in view of the description in the last sentence of paragraph [0003] of Baguisi et al.

Consequently, Applicants respectfully requests that this rejection be withdrawn.

CONCLUSION

With regard to the rejection under 35 U.S.C. § 102, the reference of Baguisi et al. does disclose the limitations of present claims, use of avian testes from an adult avian aged up to 70 weeks (e.g., aged up to 20 weeks, or aged 2-10 weeks).

With respect to the rejection under 35 U.S.C. § 103, since the reference of Baguisi et al. and Shinohara et al. do not show that the presently claimed invention would have been predictable and, indeed, there is evidence to the contrary, as discussed above, a denial of the

unobviousness of the present claims is a result of an improper hindsight reconstruction of a claimed invention.

Therefore, in view of the foregoing remarks, Applicants respectfully request reconsideration and reexamination of this invention and the timely allowance of the pending claims.

If there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

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